REMARKS

Applicants hereby request a telephone interview with the Examiner, prior to action on this case.

1. Applicants have submitted a new abstract referring to DNA encoding a growth hormone antagonist. Since a method of treatment is now also claimed, reference to such a method is included in the abstract.

2. Applicants have amended Fig. 9 as proposed by the Examiner, and corrected the specification references to Figs. 4, 8 and 9.

3. With regard to incorporation by reference, the Examiner concedes that "nonessential subject matter" may be incorporated by reference to even nonpatent publications. Because "mere reference" to another application, patent or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by 35 USC 112, first paragraph, In re de Seversky, 474 F.2d 671, 177 USPQ 144 (CCPA 1973)", as a matter of prudence, applicants formally incorporated by reference "all patents and publications cited in this specification". However, that is not an admission that any, let alone all, of the referred-to material is "essential".

The Examiner calls upon applicants to determine what material is "essential". Applicants do not believe that any of it is "essential". If the Examiner rejects the claims for lack of enablement, and, in answering that rejection, applicants rely on a reference that cannot be used as a source of "essential material", then at that point the Examiner may require applicants to copy the essential material (identified as such by the Examiner) from the reference to the specification.

4. No claims were rejected on prior art grounds, so it is assumed that the invention has been deemed patentable over the prior art.

5. All examined claims have been cancelled, therefore

mooting the enablement and indefiniteness rejections.

Claim 10 is a generic claim to a DNA molecule encoding a polypeptide with growth hormone receptor antagonist activity. This new polypeptide is defined so as to be, either, in essence, the polypeptide recited in a patented claim (claim 1 of USP 5,350,836) or the polypeptide recited in an allowed claim (claim 49 of 08/313,505). Claim 1 of the '836 patent covered

> A vertebrate growth hormone in which the amino acid position in said vertebrate growth horomone corresponding to amino acid Gly 119 of bovine growth hormone is deleted or substituted with an amino acid, said vertebrate growth hormone having growth hormone antagonist activity.

Thus, it covers all single substitution mutants of vertebrate growth hormones wherein the mutation was at the residue corresponding to bGH Gly119.

Claim 49 of 08/313,505 was written to avoid overlap with claim 1 of the '836 patent, in that it required a difference from a first reference vertebrate growth hormone "at one or more of the remaining amino acid positions", i.e., positions other than the one corresponding to bGH 119. Claim 49 reads as follows:

> A polypeptide which comprises an amino acid sequence which
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> (A) is at least 50% identical with the sequence of a first reference vertebrate growth hormone, and
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> (B) differs therefrom solely in that
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> (I) the amino acid position corresponding to amino acid Gly119 of bovine growth hormone is substituted with an amino acid other than alanine, and either
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> (II) at one or more of the remaining amino acid positions it is characterized by
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> (a) a substitution of a conservative replacement amino acid for the corresponding first reference

vertebrate growth hormone residue, or

(b) a substitution of a non-conservative replacement amino acid for the corresponding first reference vertebrate growth hormone residue where

(i) a second reference vertebrate growth hormone exists for which the corresponding amino acid is a non-conservative substitution for the corresponding first reference vertebrate growth hormone residue, and/or

(ii) the binding affinity for the first reference vertebrate growth hormone's receptor of a single substitution mutant of the first reference vertebrate growth hormone, wherein said corresponding residue, which is not alanine, is replaced by alanine, is at least 10% of the binding affinity of the wild-type first reference vertebrate growth hormone,

or

(III) it differs from the sequence of said first reference hormone by (a) one or more deletions of residues which are not part of the alpha helixes of said reference vertebrate growth hormone corresponding to helices 1(7-34), 2(75-87), 3(106-127) and 4(152-183) of porcine growth hormone, each deleted residue furthermore not being a conserved residue in the vertebrate GH family, or (b) one or more deletions of residues found in said first reference vertebrate growth hormone but deleted in a second reference vertebrate growth hormone,

or both (II) and (III);

said polypeptide having growth hormone receptor antagonist activity.

New claim 10 covers DNA molecules encoding both sorts of polypeptides, i.e., those encoding the single substitution

mutants of claim 1 of the '836 patent, and DNA molecules encoding the multiple substitution mutants of claim 49 of the '505 application.[1] Note that paragraphs (B)(II)(c) and (B)(II)(d) of new claim 9 correspond to (III)(a) and (III)(b) of claim 49 of the '505 application.

Since claim 10 is drawn to a DNA molecule encoding either a polypeptide which is the subject of a patented claim, or one which is subject of an allowed claim (save for its omission of one embodiment of the patented claim), it is clear that it must be considered patentable as well, for the reasons developed during the prosecution of the '836 patent and of the '505 application. We wish to note that claim 49 of the '505 aplication was approved of, not only by Examiner Carlson, but also by SPE Vasu Jagannathan, BPS Richard Schwartz, and QCS Robert Hill. Full faith and credit[2] should be given to the finding that the polypeptides of claim 1 are USP 5,350,836 and claim 49 of the allowed '505 application are patentable. Since designing DNA encoding such polypeptides is straightforward (see specification, p. 30), there is no reason to reject the new claims for lack of enablement or for indefiniteness.

New claims 12-39 conform to allowed claims 50-51, 53-61, 63-79 of Serial No. 08/313,505. In the latter prosecution, Vasu Jaganathan, Richard Schwartz, Robert Hill, and Karen Carlson reviewed applicants' arguments and evidence concerning enablement and agreed that applicants were entitled to the claims, as there allowed, to growth hormone mutants which act as growth hormone

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[1] However, the polypeptide recited in new claim 9 differs from that of claim 1 of the '836 patent in that it does not include mutants in which the bGH G119 equivalent is deleted.

[2] MPEP §704, "Previous Examiner's Search", provides that an examiner who takes over an application is to give "full faith and credit" to the search and action of the prior examiner. To the extent that common issues are raised, sound administration justifies a similar practice vis-a-vis prosecution of a daughter application.

antagonists. The instant claims differ from those allowed in the prior proceeding only in that they are directed to DNA encoding the allowed polypeptides.

New claim 11 limits the DNA molecules of claim 10 to those encoding mutants in which the mutation of the GH-related sequence is limited to substitutions.

Claims 12-39 should therefore be allowed for the same reasons as claim 9 above.

Note that independent DNA claim 29 corresponds to independent polypeptide claim 69 of the '505 application.

New claims 40-41 are DNA molecule claims reciting the presence of a promoter (40), or a regulatable promoter (41), in accordance with page 30, lines 21-33.

New claims 42-43 recite that the DNA molecule is a retroviral vector (claim 42; see p. 37, lines 1-4) or a linearized DNA (claim 43; see p. 36, lines 31-36). Claim 44 is to a transformed cell (see page 30, lines 20-21) and claim 45 to a nonhuman transgenic animal (see page 36, lines 29-31).

New claims 46-60 relate to therapeutic use of the DNA by introducing DNA encoding the GH antagonist into the animal. Claim 46 generically recites the use of the expression vector of claim 40 for preventing conditions caused by excessive growth hormone activity (e.g., acromegaly, gigantism), or exacerbated by growth hormone activity (e.g., diabetes, certain cancers). Such methods are disclosed in the specification. For "gene therapy", see page 7, lines 19-24 and page 37, lines 4-8. For therapeutic purposes, see page 31, line 15 to page 34, line 25, page 3, line 27 to page 6, line 31, page 7, line 29 to page 8, line 2, page 8, lines 9-17, page 8, line 36 to page 11, line 7, page 13, line 34 to page 14, line 9, and Examples 6 and 8.

New method claim 61 is based on page 4, lines 26-30 of the parent application. Since the parent application was incorporated by reference (page 1, lines 5-15), applicants have the right to insert this material into the present specification.

New DNA molecule claim 62 is similar to claim 10, but permits insertions as well as deletions. New paragraphs (e) and (f), relating to insertions, parallel paragraphs (c) and (d), relating to deletions. The Examiner will appreciate if two sequences are aligned, and a residue in sequence A corresponds to a gap in sequence B, one can say either A differs from B by making an insertion in B, or that B differs from A by making a deletion in A.

Deletions and insertions were expressly contemplated in the specification. See, e.g., page 17, lines 35-37, page 18, lines 2-3, page 23, lines 9-11, page 24, lines 6-8 and 12-14, page 25, lines 2-4 and 14-16.

Pursuant to MPEP §821.04, such method claims are properly joined with the DNA claims if the method claims are dependent on the DNA claims and the DNA claims are themselves patentable over the prior art.

6. In the interest of furthering prosecution, we briefly comment on the method-of-use claims. New claim 46 recites "preventing a condition of a human or animal subject caused by excessive growth hormone activity". While the term "preventing" is not formally defined, it is customarily given the meaning that there is a statistically significant difference between the incidence or severity of the condition in treated and untreated subject. Customarily, many vaccines are said to "prevent" the corresponding disease even though such prevention is not absolute.

Acromegaly and gigantism are considered conditions characterized by excessive, and, more particularly, elevated, growth hormone activity.

New claim 46 also recites "treating a condition of a human or animal subject exacerbated by growth hormone activity". The term "treatment" is defined at page 31, lines 25-35:

> The term "treatment" as used herein with reference to a disease is used broadly and

> is not limited to a method of curing the disease. The term "treatment" includes any method that serves to reduce one or more of the pathological effects or symptoms of a disease or to reduce the rat of progression of one or more of such pathological effects or symptoms. Diseases that may be treated by the methods of the invention are diseases characterized by one or more of the following criteria: elevated levels of GH production, elevated levels of GHR production, and elevated cellular response to GHRs to GH.

Applicants also state, on page 13, line 34 to page 14, line 6, that:

> The present invention also relates to methods of using such antagonists for treating diseases and disorders which are regulated wholly or partly by GHRs. Such diseases and disorders would include (a) those in which hGH action was excessive due to <u>normal</u> sensitivity of the tissues to increased levels of hGH (such as acromegaly and diabetes) and (b) those in which hGH action was excessive due to <u>increased</u> sensitivity of the tissues (as might result from increased GHR density) to normal levels of hGH (as in cancer and restenosis).

Thus, a GH antagonist may be used to treat diabetes, even if the antagonist does not itself lower blood glucose levels,[3] because patients with longstanding diabetes commonly develop

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[3] A direct effect is possible, see page 9, line 31 to page 10, line 15.

diabetic retinopathy, nephropathy (glomerulosclerosis), angiopathy and neuropathy and the rate of development of these sequelae is mediated by GH. Normal levels of GH may thus be said to "exacerbate" the condition.

Likewise, even though the GH antagonist does not kill cancer cells, it may be useful in treating a cancer because (a) the rate of growth of the cancer is dependent on the level of GH activity, or (b) the cancer cells are secreting GH, thereby causing problems attributable to elevated GH activity.

Respectfully submitted,

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Enclosures
-Fig. 9
-Abstract of the Disclosure
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